Frequency of infraposition and missing contact points in implant-supported restorations within natural dentitions over time: A systematic review with meta-analysis

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Abstract: OBJECTIVES The aim of this systematic review was to assess clinical evidence on adverse effects of osseointegrated implants placed among natural teeth of a residual dentition. METHODS Seven databases were searched without restrictions up to January 2018 for clinical studies on implant infraposition (IIP) or proximal contact point (PCP) loss to the adjacent teeth. After duplicate selection, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of odds ratios (OR) or mean differences (MD) and their 95% confidence intervals (CI) were performed, followed by meta-regression and sensitivity analyses. RESULTS A total of 27 nonrandomized studies with 1,572 patients (mean age 42.2 years/51.2% female) followed up to 18.5 years after implant placement were included. The pooled %prevalence of IIP was 50.5% (nine studies; 95% CI = 26.3-74.5%), and the pooled IIP extent was 0.58 mm (six studies; 95% CI = 0.33-0.83 mm), while IIP > 1 mm was seen for 20.8% of placed implants (five studies; 95% CI = 8.3-37.1%), and male patients were less prone to IIP than female patients (three studies; OR = 0.30; 95% CI = 0.10-0.88; p = 0.03). The pooled %prevalence of PCP loss was 46.3% (nine studies; 95% CI = 32.3-60.6%), with increase through observation time (two studies; OR = 1.09; 95% CI = 1.03-1.16; p = 0.004) and predilection for mesial PCPs (five studies; OR = 2.25; 95% CI = 1.06-4.77; p = 0.03). However, the quality of evidence was very low due to bias. CONCLUSIONS Patients and doctors need to be aware that long-term adverse effects of dental implants among natural teeth can be observed in terms of IIP and PCP loss to the adjacent teeth.

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SUPPLEMENT ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Frequency of infraposition and missing contact points in implant-supported restorations within natural dentitions over time: A systematic review with meta-analysis

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Abstract

Objectives: The aim of this systematic review was to assess clinical evidence on adverse effects of osseointegrated implants placed among natural teeth of a residual dentition.

Methods: Seven databases were searched without restrictions up to January 2018 for clinical studies on implant infraposition (IIP) or proximal contact point (PCP) loss to the adjacent teeth. After duplicate selection, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of odds ratios (OR) or mean differences (MD) and their 95% confidence intervals (CI) were performed, followed by meta-regression and sensitivity analyses.

Results: A total of 27 nonrandomized studies with 1,572 patients (mean age 42.2 years/51.2% female) followed up to 18.5 years after implant placement were included. The pooled %prevalence of IIP was 50.5% (nine studies; 95% CI = 26.3–74.5%), and the pooled IIP extent was 0.58 mm (six studies; 95% CI = 0.33–0.83 mm), while IIP > 1 mm was seen for 20.8% of placed implants (five studies; 95% CI = 8.3–37.1%), and male patients were less prone to IIP than female patients (three studies; OR = 0.30; 95% CI = 0.10–0.88; $p = 0.03$). The pooled %prevalence of PCP loss was 46.3% (nine studies; 95% CI = 32.3–60.6%), with increase through observation time (two studies; OR = 1.09; 95% CI = 1.03–1.16; $p = 0.004$) and predilection for mesial PCPs (five studies; OR = 2.25; 95% CI = 1.06–4.77; $p = 0.03$). However, the quality of evidence was very low due to bias.

Conclusions: Patients and doctors need to be aware that long-term adverse effects of dental implants among natural teeth can be observed in terms of IIP and PCP loss to the adjacent teeth.

KEYWORDS

adverse effects, clinical research, dental implants, meta-analysis, osseointegration, systematic review

1 | INTRODUCTION

1.1 | Rationale

Osseointegrated dental implants have become an integral part in contemporary dentistry as a popular treatment choice to replace one or more missing teeth. They have high survival rates after 5–10 years (Jung, Zembic, Pjetursson, Zwahlen & Thoma, 2012; Moraschini, Poubel, Ferreira & Barboza Edos, 2015) or 15 or more years, even though research on their long-term performance focuses mostly on bone remodeling and clinical response parameters (Bergenblock,

Andersson, Fürst & Jemt, 2012; Dierens, Vandeweghe, Kisch, Nilner & De Bruyn, 2012; Jemt, 2008).

However, a wide variety of biological, technical, and aesthetic complications that are frequently seen has been reported (Albrektsson & Donos, 2012; Wittneben et al., 2014) with estimated cumulative complication rates around 7% after 5 years (Jung et al., 2012). Additionally, most complications described in the literature pertain to technical or biological failures of the osseointegrated fixture and its supraconstruction or on tissue destruction due to peri-implantitis. Aesthetic parameters, like soft tissue topography around the implant restoration and the position of its crown in relation to the adjacent teeth, are equally significant factors for the success of treatment from an aesthetic point of view (Chang, Ödman, Wennström & Andersson, 1999) and especially for implants placed in the anterior maxilla—yet, receive less attention.

Additionally, the absence of maxillary permanent anterior teeth due to trauma or congenital aplasia and the subsequent impact on the person's quality of life means that sometimes the recipients of dental implants might be young patients with residual growth potential. The use of implants in growing patients has been studied both in humans (Thilander, Ödman, Gröteborg & Friberg, 1994) and animals (Ödman, Grondahl, Lekholm & Thilander, 1991), leading to the observation that dental implants behave like ankylosed teeth and are capable of following neither the growth of the jaws nor the continuous eruption of adjacent natural teeth (Iseri & Solow, 1996; Thilander et al., 1994). This most often results in a discrepancy in the occlusal plane, manifesting clinically in an implant infraposition (IIP) compared with the crowns of the adjacent teeth. However, similar observations of IIP have also been done among mature adult patients (Bernard, Schatz, Christou, Belser & Kiliaridis, 2004; Thilander, Ödman & Jemt, 1999) with little to no active growth potential, which could lead to aesthetic impairment and ultimately the need to replace the implant-supported restoration.

Another post-treatment complication that has been reported increasingly during the last decade is the loss of the proximal contact point (PCP) between the restored implant's crown and the adjacent natural teeth (Byun, Heo, Ahn & Chang, 2015; Wei, Tomotake, Nagao & Ichikawa, 2008; Wong, Wat, Pow & Leung, 2015). It has been postulated that natural teeth move in vertical and sagittal directions both during active adolescent growth of the jaws, but also during the slow growth that can be seen in both young and mature adults (Oesterle & Cronin, 2000). Additionally, the position of the teeth within the dental arch is not stable and a number of factors, including among others location, tooth type, gender, age, vitality of adjacent teeth, and the strength of occlusal forces, have been proposed as important in both PCP tightness and PCP loss (Pang, Suh, Kim, Park & Jung, 2017). At the same time, PCP loss has been associated with food impaction in the interdental area, with subsequent patient dissatisfaction (Jeong & Chang, 2015), and with periodontal disease (Jernberg, Bakdash & Keenan, 1983).

1.2 | Aim

Current evidence on long-term complications of implants functioning among natural teeth that are related to their osseointegration and ankylotic nature is limited. Therefore, the aim of this systematic review was to assess in an evidence-based manner the existing data from longitudinal studies and try to answer the question:

> *What are the adverse effects of osseointegrated dental implants functioning among natural teeth in residual dentitions of adolescent and adult patients and especially the rate and extent of IIP and PCP loss?*

2 | MATERIAL AND METHODS

2.1 | Protocol and registration

The review's protocol was made a priori following the PRISMA-P statement (Shamseer et al., 2015), registered in PROSPERO (CRD42018086404), and all post hoc changes were appropriately noted. This systematic review was conducted and reported according to Cochrane Handbook (Higgins & Green, 2011) and PRISMA statement (Liberati et al., 2009), respectively.

2.2 | Eligibility criteria

According to the Participants-Intervention-Comparison-Outcome-Study design (PICOS) schema, we included randomized or non-randomized clinical studies on human patients of any age, sex, or ethnicity with at least one osseointegrated dental implant placed (including its restoration) among natural teeth. The primary outcome of this systematic review was the IIP of the osseointegrated implant (and its suprastructure) compared with adjacent teeth, while the secondary outcome pertained to loss of the PCP of the implant's crown with the adjacent natural tooth. Excluded were nonclinical studies, case reports, animal studies, studies on patients with systemic diseases or syndromes, studies on implant-supported overdentures or tooth-and-implant restorations, studies on surgical or short-term (<6 months) outcomes, and studies with nonrelevant outcomes.

2.3 | Information sources and literature search

Seven electronic databases were systematically searched by one author (SNP) without any limitations from inception up to 10 January 2018 (Supporting Information Appendix S1): MEDLINE (searched via PubMed), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, EMBASE, Virtual Health Library, Scopus, and Web of Knowledge. Additionally, five sources (Google Scholar, International Standard Registered Clinical/soCial sTudy Number Registry, Directory of Open Access Journals, Digital Dissertations, metaRegister of Controlled Trials, and ClinicalTrials.gov) and the reference/citation lists of included trials were manually

searched for any additional trials. No limitations concerning publication language, publication year, or publication status were applied.

2.4 | Study selection

The eligibility of identified studies was checked sequentially from their title, abstract, and full-text against the eligibility criteria by one person (SNP) and was subsequently checked independently by a second one (TE), with any conflicts being resolved by a third person (CHFH).

2.5 | Data collection and data items

Study characteristics and numerical data were extracted from included studies independently by two authors (SNP, TE) using predefined and piloted extraction forms including: (a) study characteristics (design, clinical setting, country), (b) patient characteristics (age, sex, or smoking at implant placement and orthodontic treatment prior to implant placement), (c) number and type of implants, (d) type and localization of prosthetic restoration, (e) analyzed sample, and (f) outcome details (type of adverse effect, nature, measurement method, timing, and any treatments for these adverse effects). Piloting of the forms was performed during the protocol stage until over 90% agreement was reached. Missing or unclear information was calculated, whenever possible. Any individual patient data provided in an included study were extracted and reanalyzed firsthand (Supporting Information Appendix S2).

2.6 | Risk of bias in individual trials

The risk of bias of included randomized trials was to be assessed using Cochrane's risk of bias tool (Higgins & Green, 2011); the risk of bias of included nonrandomized studies was assessed using a modified Newcastle-Ottawa scale for cohort studies (Wells et al., 2010) at outcome level as, as guided by the Cochrane Handbook (Higgins & Green, 2011).

2.7 | Outcomes and data synthesis

The primary outcome of IIP was measured as binary yes/no variable (existence of IIP), as continuous variable (extent of IIP in mm), and as categorical variable according to magnitude, for which most authors took the 1 mm cut-off to denote considerable IIP. The secondary outcome of PCP loss was measured as binary yes/no variable (lack of PCP). These outcomes were reported either on patient level or on implant/tooth level and, as the latter was more often reported, this was adopted as main analysis unit.

Initially, the pooled % event rate of IIP or PCP loss and the pooled IIP extent in mm was calculated in an indirect explorative analysis across studies (1-group pooling). Subsequently, direct comparisons were made from within- and across-studies data regarding the influence of various patient-, implant-, or study-related characteristics using Relative Risks (RR) for binary/categorical or Mean Differences (MD) for continuous outcomes with the corresponding 95% Confidence Intervals (CI) (2-groups' pooled comparisons). In case of identified studies reporting Odds Ratios (OR) adjusted for confounders, these were used instead of RRs to improve effect precision. Statistically significant ORs/RRs were translated clinically with the Number Needed to Treat (NNT).

As adverse effects of dental implants among natural teeth are bound to be affected by the person's residual growth potential, the masticatory habits, issues pertaining to the implant or its prosthetic reconstruction, and the periodontal or functional status of adjacent teeth, a wide variation of true effects was expected to exist. Therefore, a random-effects model was judged a priori to be appropriate to calculate the average of the distributions of effects, based on biological, clinical, and statistical grounds (Papageorgiou, 2014a). Novel random-effects model estimators were used instead of the more widely known DerSimonian and Laird (1986) estimator, based on contemporary guidelines and software availability, due to their improved performance. The bootstrapped-DerSimonian-Laird method (Petropoulou & Mavridis, 2017) was used for indirect pooling of IIP/PCP loss event rates, and the Paule–Mandel method (Veroniki et al., 2016) was used for indirect pooling of IIP extent and direct meta-analyses of OR, RR, and MD.

The extent and impact of between-study heterogeneity were assessed by inspecting the forest plots and calculating the τ^2 (absolute heterogeneity) and the I^2 (relative heterogeneity), respectively; I^2 defines the proportion of total variability in the result explained by heterogeneity, and not chance (Higgins, Thompson, Deeks & Altman, 2003). Heterogeneity was roughly categorized as low, moderate, and high according to I^2 values of 25, 50, and 75% (Higgins et al., 2003), although the heterogeneity's localization on the forest plot was also examined. Additionally, the 95% CIs around τ^2 and I^2 were calculated (Ioannidis, Patsopoulos & Evangelou, 2007) to quantify our uncertainty around these estimates. Ninety-five per cent predictive intervals were calculated for meta-analyses of ≥3 trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting, which is crucial for the correct interpretation of random-effects meta-analyses (IntHout, Ioannidis, Rovers & Goeman, 2016). All analyses were conducted in Stata SE version 14.2 (StataCorp LP, College Station, Texas, USA) by one author (SNP) with the data made freely available in Zenodo (Papageorgiou, Eliades & Hämmerle, 2018). A two-sided $p < 0.05$ was considered significant for hypothesis-testing, except for $p < 0.10$ used for tests of between-studies or between-subgroups heterogeneity (Ioannidis, 2008).

2.8 | Additional analyses and quality of meta-evidence

Possible sources of heterogeneity were a priori planned to be sought through random-effects subgroup analyses and random-effects meta-regression for meta-analyses of ≥ five studies, including: mean patient age, % male proportion of the patient sample, % of restorations in the maxilla, % of restoration in the anterior region (canine to canine), and the length of follow-up. Additional analyses

for subgroups, meta-regressions, and reporting biases were planned, but were not conducted, due to lack of available studies (Supporting Information Appendix S2).

The overall quality of clinical recommendations for outcomes addressed by direct evidence (analyses with OR, RR, or MD) was rated using the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, as very low, low, moderate, or high (Guyatt, Oxman, Schünemann, Tugwell & Knottnerus, 2011) and a Summary of Findings table was constructed using the improved format proposed by Carrasco-Labra et al. (2016) and recent guidance on incorporating nonrandomized studies (Schünemann et al., 2018). The minimal clinical important (Norman, Sloan & Wyrwich, 2003), large, and very large effects were defined as half, one, and two standard deviations (using the average standard deviation for an outcome across included studies), respectively. Arbitrary cut-offs of 1.5, 2.0, and 5.0 (Schünemann, Brozek & Oxman, 2009) were adopted for OR and RR. The produced forest plots were augmented with contours denoting the magnitude of the observed effects (Papageorgiou, 2014b) to visually gauge heterogeneity, clinical relevance, and imprecision.

Robustness of the results was planned a priori to be checked with sensitivity analyses based on (a) inclusion/exclusion of trials with methodological shortcomings, (b) improvement of the GRADE classification, and (c) inclusion/exclusion of large-scale studies.

3 | RESULTS

3.1 | Study selection

The literature search yielded a total of 579 hits (Figure 1), 166 of which proceeded to full-text assessment after eliminating duplicates and ineligible studies by title or abstract (Supporting Information Appendix S3). Finally, a total of 34 papers were identified as eligible for inclusion in the present systematic review. After pooling multiple papers relating to the same study, a total of 27 unique clinical studies published in Dutch, English, Japanese, or Portuguese between 1994 and 2017 were included. Apart from data from published reports, a total of four authors of identified studies were contacted for raw data, from which, however, none responded up to now (Supporting Information Appendix S4).

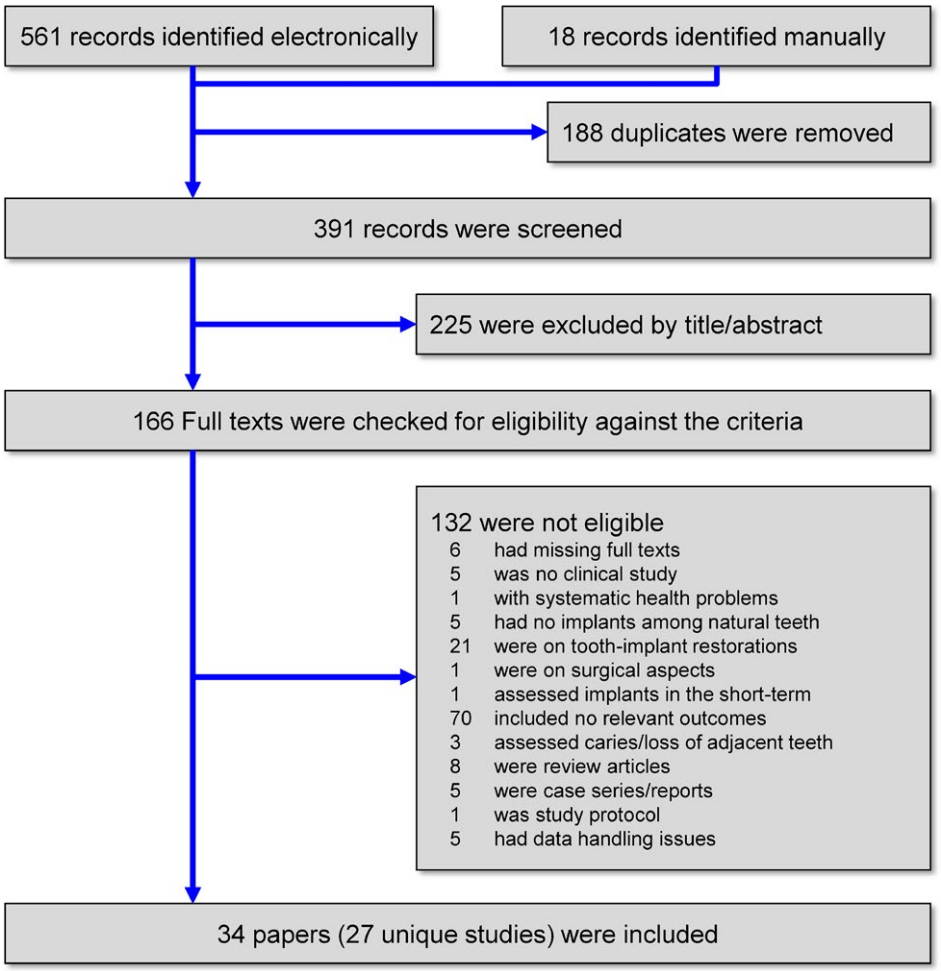

FIGURE 1 PRISMA flow diagram for the identification and selection of eligible studies

TABLE 1 Patient and implant characteristics of included studies

No.	Study ID	Design; setting; country (ISO Alpha 3)	Patients (F/M); mAge (R) in years	Smok%	Ortho%	Imps	Restoration	Max%	ANT%
1	Avivi-Arber (1996)	uNRS; Uni; CAN	41 (19/22); 33.5 (14.5–63.9)	NR	NR	49 Imps (NB)	SC	71	63
2	Bergenblock (2012), Andersson (2013)[a]	rNRS; Clinic; SWE	57 (25/32); 31.9 (15.0–57.0)	8/27	9%	65 Imps (NB)	SC	>50	77
3	Bernard (2004)	rNRS; Uni; CHE	G1: 14 (9/5); 18.4 (15.5–21.0) G2: 14 (9/5); 43.6 (40.0–55.0)	NR	NR	G1-2: 40 Imps (ST)	SC	100	100
4	Bonde (2013)[b]	rNRS; Uni; DNK	51 (NR); NR	NR	NR	55 Imps (NB)	SC	NR	NR
5	Brahem (2017)	uNRS; Uni; DNK	G1: 20 (13/7); 33.8 (G1-2 18.0–61.0) G2: 37 (24/13); 27.5 (G1-2 18.0–61.0)	NR	In G2 (43% Ret)	G1-2: 89 Imps (NR)	SC	100	100
6	Byun (2015)[c], Jeong (2015)	rNRS; Uni; KOR	94 (44/50); 56.0 (27.0–83.0)	NR	NR	188 Imps (NR)	SC/FIP	48	6
7	Chang (2012)	rNRS; Uni; SWE	31 (13/18); 40.0 (19.0–71.0)	NR	NR	33 Imps (AT)	SC	100	58
8	Cosyn (2012)	rNRS; Uni/practice; BEL	97 (37/60); 51.0 (23.0–80.0)	NR	NR	97 Imps (NB)	SC	100	66
9	Dierens (2013)[d], Dierens (2016)	rNRS; clinic; SWE	21 (9/12); 23.0 (33.0–58.0)	4%	NR	24 Imps (NB)	SC	100	83
10	Ekfeldt (2011, 2017)	rNRS; clinic; SWE	30 (NR); 23.0 (17.0–72.0)	3%	NR	30 Imps (NB)	SC	84	6
11	Fukunishi (2016)	uNRS; clinic; JAP	135 (83/52); 61.6 (NR)	NR	NR	185 Imps (BM)	SC	0	0
12	Gjelvold (2017)	rNRS; clinic; SWE	87 (36/51); 21.4(17.0–68.0)	17%	67%	126 Imps (DE)	SC	81	83
13	Jamilian (2015)	rNRS; Uni; IRN	10 (5/5); 20.0 (NR)	NR	Prb. 100%	14 Imps (NR)	SC	100	100
14	Jemt (2007)[e], Jemt (2008)	rNRS; clinic; SWE	25 (7/18); 26.9 (NR)	NR	NR	56 Imps (NB)	SC	100	100
15	Koori (2010)	rNRS; practice; JAP	105 (67/38); NR (20.0–78.0)	NR	NR	353 Imps (misc)	SC/FIP	26	NR
16	Kuijpers (2006)	rNRS; clinic; NLD	8 (3/5); 16.6 (12.1–18.9)	NR	88%	11 Imps (NR)	SC	100	100
17	Nilsson (2017)	pNRS; hosp; SWE	52 (29/23); 22.0 (17.0–52.0)	15%	Few	69 Imps (ST)	SC	93	100
18	Pang (2017)	pNRS; Uni; KOR	150 (83/67); 58.4 (21.0–79.0)	NR	NR	384 (misc)	SC/FIP	42	0
19	Ren (2016)	pNRS; Uni; CHN	20 (10/10); 40.0 (NR)	NR	NR	20 Imps (NB)	SC	0	0
20	Ryu (2016)	uNRS; Uni; KOR	28 (14/14); 60.0 (21.0–78.0)	NR	NR	62 Imps (NR)	SC/FIP	NR	NR

(Continues)

TABLE 1 (Continued)

No.	Study ID	Design; setting; country (ISO Alpha 3)	Patients (F/M); mAge (R) in years	Smok%	Ortho%	Imps	Restoration	Max%	ANT%
21	Schwartz-Arad (2015)	rNRS; clinic; ISR	35 (14/21); 29.2 (NR)	NR	NR	35 (NR)	SC	100	100
22	Son (2009)	uNRS; Uni; KOR	196 (NR); NR (NR)	NR	NR	NR; NR	NR	NR	0
23	Thilander (1994)[f], Thilander (1999), Thilander (2001)	rNRS; Uni; SWE	15 (7/8); 15.3 (13.2–19.3)	NR	100%	27 Imps (NB)	SC	70	67
24	Varthis (2016)	rNRS; Uni/practice; USA	128 (NR); NR (19.0–91.0)	NR	NR	174 Imps (misc)	SC	NR	NR
25	Vilhjálmsson (2013)	pNRS; Uni; NOR	26 (11/15); 34.8 (20.0–56.0)	35%	NR	28 Imps (NB/AT)	SC	100	100
26	Wang (2016)[g]	rNRS; practice; AUS	NR; NR	NR	NR	5621 Imps (NR)	SC/FIP	NR	NR
27	Wong (2015)	rNRS; Uni; HKG	45 (27/18); 45.0 (27.0–74.0)	NR	None	(NB)	SC/FIP	NR	0

ANT: in anterior region (canine to canine); AT: Astra Tech; BM: Biomet; DE: Dentsply; F/M: female/male; FIP: fixed implant prosthesis; FR: Friatec; G: group; Hosp: hospital; Imp: implant; mAge: mean age; Max: in the maxilla; Misc: miscellaneous; NB: Nobel Biocare; NR: not reported; Ortho: had orthodontic treatment prior to implant treatment; pNRS: prospective non-randomized study; Prb.: probably; R: range of included ages; Ret: retention regimen; rNRS: retrospective non-randomized study; SC: single crown; Smok: smokers at baseline; ST: Straumann; Uni: university; uNRS: unclear design of non-randomized study (probably retrospective); WA: Warantec.

[a]Follow-up publication of previous studies (Andersson B. Implants for single-tooth replacement. A clinical and experimental study on the Brånemark Cera-One system. Swed Dent J 1995; Suppl. 108:7–41/ Andersson B, Ödman P, Lindvall A-M, Brånemark P-I. Cemented single crowns on osseointegrated implants after 5 years: results from a prospective study on CeraOne abutments. *Int J Prosthodont* 1998; 11:212–218). [b]follow-up publication of previous study (Bonde MJ, Stokholm R, Isidor F, Schou S. Outcome of implant-supported single-tooth replacements performed by dental students. A 10-year clinical and radiographic retrospective study. *Eur J Oral Implantol* 2010;3:37–46). [c]the subsequent identified study Jeong 2015 was judged to have the same cohort according to the patient/methods description given; results regarding mesiodistal tooth-to-implant distance and contact point height are given only at the follow-up appointment and not at baseline and therefore are not reported here. [d]follow-up publication of previous study (Dierens M, Vandeweghe S, Kisch J, Nilner K, De Bruyn H. Long-term follow-up of turned single implants placed in periodontally healthy patients after 16-22 years: radiographic and peri-implant outcome. *Clin Oral Implants Res* 2012;23(2):197–204). The subsequent identified study Dierens 2016 also used the same patient cohort, but reported only infrapositions that were severe enough to lead to crown replacement and therefore the Dierens 2013 publication is primarily used here. [e]follow-up publication of previous report (Jemt T, Ahlberg G, Henriksson K, Bondevik O. Changes of anterior clinical crown height in patients provided with single-implant restorations after more than 15 years of follow-up. *Int J Prosthodont* 2006;19:455–461). The subsequent identified study Jemt, 2008 also used the same patient cohort, but reported infrapositions in terms of crown replacement need and therefore the Jemt 2007 study is primarily used here. [f]two subsequent identified studies Thilander 1999 and Thilander 2001 reported results from the same cohort of patients, but with different follow-up. [g]various types of fixed restorations were included that were supported by implants, teeth, or both. Only single implant crowns, single-implant cantilever crowns, and three-unit implant-supported fixed restorations are included here.

TABLE 2 Outcome details of the included studies

No.	Study ID	Analyzed sample	Outcome	Outcome details	mFU (R) in years[a]	Treatment
1	Avivi-Arber (1996)	35/41 Pats; 42/49 Imps	IIP	bin; clin; Pat/Imp-L	4.0 (1.0–8.0)	Replacement
2	Bernard (2004)	All	IIP	cont; Rx; Pat/Imp-L	4.3 (1.1–9.1)	NR
3	Bergenblock (2012), Andersson (2013)	Prb all	IIP	cat (Jemt 2007); photo.; Pat/Imp-L; 4 obs	NR (17–19)	Replacement
4	Bonde (2013)	42/51 Pats; 46/55 Imps	IIP	bin; clin; Imp-L	10.0 (8.0–12.0)	NR
5	Brahem (2017)	Prb all	IIP MD displacement at crown	cat (Jemt 2007); 3D superimposition.;Imp-L cat; clin	7.0 (NR)	NR
6	Byun (2015), Jeong (2015)	Prb all	PCP loss	cat (O'Leary, Badell & Bloomer, 1975); clin	4.8 (0.3–13.0)	Tx
7	Chang (2012)	31/33 Imps	IIP MD displacement at root	Rx; Imp-L Rx; Imp-L	1.0/5.0/8.0 (—)	NR
8	Cosyn (2012)	Prb all	PCP loss MD displacement at root	bin bin; clin	2.6 (1.4–3.5)	NR
9	Dierens (2013), Dierens (2016)	Prb all	IIP	cat; clin/phot	18.0 (16.0–22.0)	NR
10	Ekfeldt (2011, 2017)	30/31 Pats/Imps	IIP	bin; NR	NR (10.0–11.0)	NR
11	Fukunishi (2016)	Prb all	PCP loss	bin; clin	5.0 (NR)	NR
12	Gjelvold (2017)	59/87 Pats; 85/126 Imps	IIP MD displacement at crown	cont; Rx; Pat/Imp-L cont; models	7.5 (3.6–11.1)	NR
13	Jamilian (2015)	All	IIP	bin; Rx; Imp-L	5.6 (NR)	NR
14	Jemt (2007), Jemt (2008)	All	IIP BP displacement at crown	cat (Jemt 2007); photo.; Imp-L; 3 obs bin; Imp-L; 3 obs	15.9 (NR)	NR
15	Koori (2010)	All	PCP loss	bin; clin; Imp-L	(0.1–10.3)	NR
16	Kuijpers (2006)	All	IIP	cont; clin/Rx; Imp-L	11.0 (9.9–12.0)	NR
17	Nilsson (2017)	All	IIP	bin; clin; Imp-L	4.5 (3.3–6.6)	Replacement
18	Pang (2017)	Prb all	PCP loss	bin; clin; Imp-L	7.0 (—)	NR
19	Ren (2016)	18/20 Pats/Imps	PCP tightness	cont; clin-app; Imp-L	1.0 (—)	NR
20	Ryu (2016)	All	PCP loss	cat (O'Leary et al., 1975); clin	5.8 (0–14.9)	NR
21	Schwartz-Arad (2015)	All	IIP	cont; clin; Imp-L	7.5 (NR)	NR
22	Son (2009)	NR	PCP loss	bin; clin	NR (0–6.0)	Composite filling; Replacement
23	Thilander (1994), Thilander (1999), Thilander (2001)	14/15 Pats; 26/27 Imps	IIP	cont; clin/Rx; Pat/Imp-L	3.0/8.0/10.0 (—)	NR
24	Varthis (2016)	Prb all	PCP loss	bin; clin/floss & Rx	(0.3–11.0)	NR
25	Vilhjálmsson (2013)	23/26 Pats	IIP	cont; Rx; Pat/Imp-L	3.0 (—)	NR
26	Wang (2016)	Prb all	PCP loss	bin; clin; Imp-L	3.1 (NR)	NR
27	Wong (2015)	Prb all	PCP loss PCP space	bin; clin-matrix; Imp-L cont; clin-matrix; Imp-L	3.9 (0.5–12.0)	NR

app: appliance specific for contact area/point/tightness/thickness measurement; bin: binary; BP: buccopalatal (or -lingual); cat: categorical; clin: clinical examination; cont: continuous; Imp: implant; IIP: infraposition of the implant restoration compared with the adjacent teeth; L: level; MD: mesiodistal; NR: not reported; obs: observers; Pat: patient; PCP: proximal contact point; photo: photographic examination; Prb: probably; Rx: radiology.

[a]Follow-up ranges given as (—) indicate that exact follow-up periods were followed in the study.

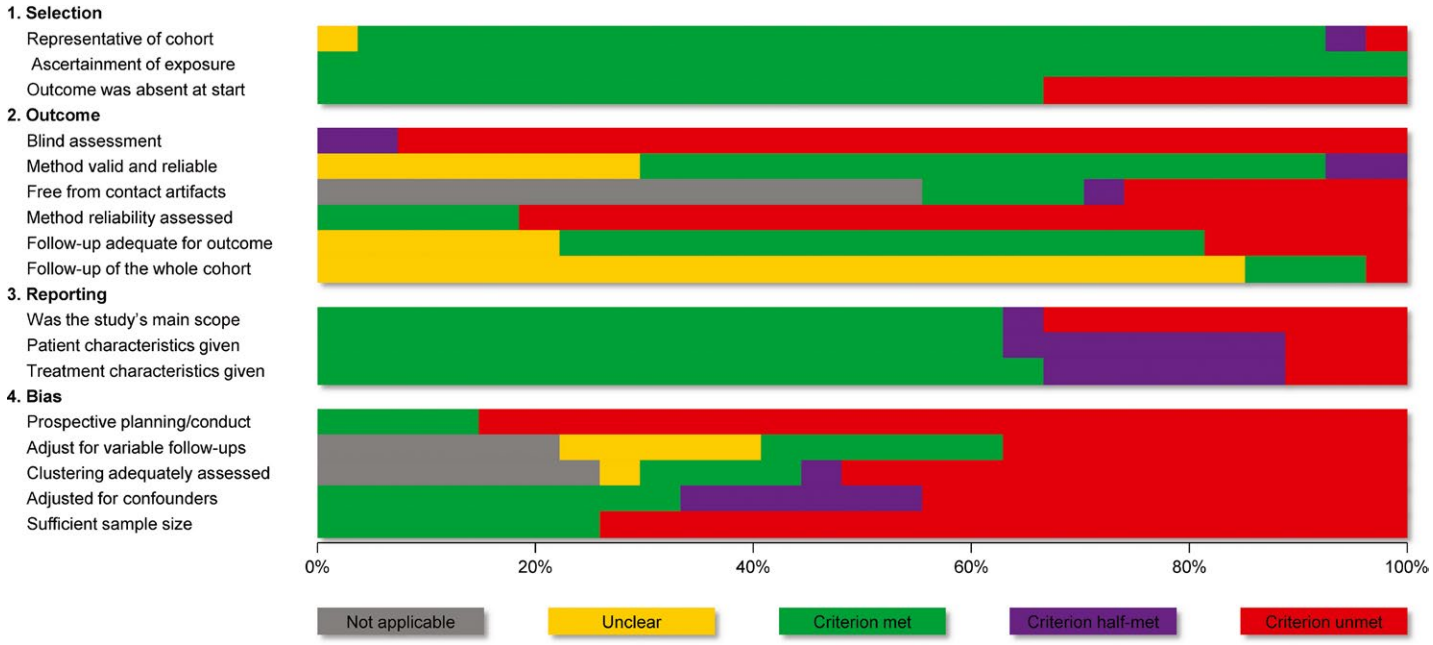

FIGURE 2 Summary of the methodological adequacy (including potential bias) of identified studies using a modified Newcastle-Ottawa tool

TABLE 3 Indirect random-effects meta-analysis across studies on the pooled event rate or values of the primary and secondary outcomes at implant/tooth/contact point level. All data sets (pertaining to different follow-ups) are extracted from each study, but only the one with the longest follow-up is included in the analysis

Outcome	Studies	Effect	95% CI	τ^2 (95% CI)	I^2, % (95% CI)	95% prediction
IIP_{binary} % event rate	9	50.5%	26.3–74.5	0.56 (NC)	95 (92–97)	10.4–90.0
$IIP_{continuous}$ extent in mm	6	0.58 mm	0.33–0.83 mm	0.08 (0.02–0.53)	88 (69–98)	0[a]–1.43 mm
IIP > 1 mm_{binary} % event rate	5	20.8%	8.3–37.1	0.14 (NC)	84 (63–93)	4.3–60.9
PCP $loss_{binary}$ % event rate	9	46.3%	32.3–60.6	0.19 (NC)	97 (96–98)	20.0–74.8

CI: confidence interval; IIP: infraposition of the implant restoration relative to adjacent teeth; NC: noncalculable; PCP: proximal contact point.
[a]Truncated at zero.

3.2 | Study characteristics

The descriptive characteristics of the 27 included studies can be seen in Tables 1 and 2. From these, none was a randomized trial, four (15%) were prospective nonrandomized studies, and the remaining 23 (85%) studies were nonrandomized studies with retrospective or unclear design. Most studies were conducted in university clinics (n = 16; 59%) or private practices (n = 8; 30%) in at least 15 different countries (with Sweden contributing the greatest with eight studies). Overall, at least 1,572 patients were included (from the 26 studies reporting patient sample) with a mean age of 42.2 years (from the 22 studies reporting age) and with 51.2% of the patients being female (from the 22 studies reporting sex). These patients had been treated with the placement of at least 7,835 implants (from the 25 studies reporting implant number) and re-examined after a median of average follow-up periods 5.7 years afterward, ranging from 1 to 18 years (from the 22 studies reporting mean follow-up). The primary outcome of IIP was the most widely-used outcome (assessed in 16 studies), followed by the secondary outcome of PCP loss (assessed in 10 studies). Other outcomes (not analyzed here) included mesiodistal movement of adjacent tooth at crown or root (2 studies each), buccolingual movement of adjacent tooth at crown (1 study), PCP space (1 study), and PCP tightness (1 study).

3.3 | Risk of bias within studies

The methodological adequacy (with possible implications for the risk of bias) of identified studies according to the modified Newcastle-Ottawa tool is given in detail in Supporting Information Appendix S5a,b and in summary in Figure 2. All included studies were found to have serious methodological issues, with the most problematic domains being the blinding of outcome assessment (completely absent in

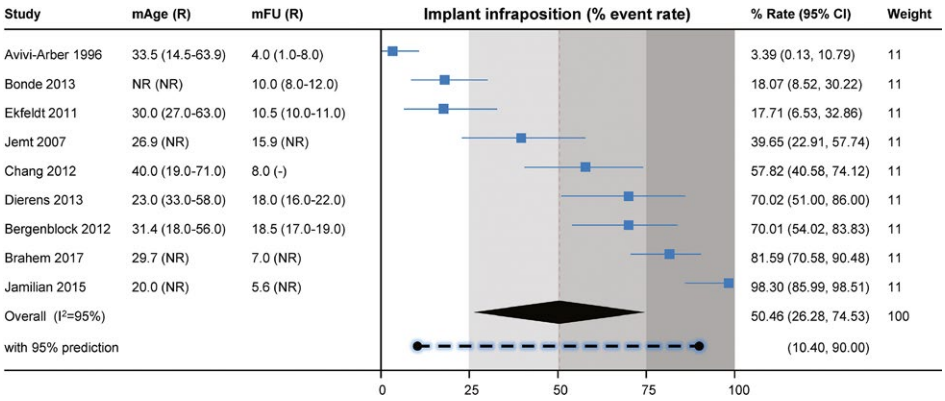

FIGURE 3 Contour enhanced forest plot of the pooled % event rate of implant infraocclusion at implant level. CI, confidence interval; mAge, mean age at implant placement in year; mFU, mean follow-up in years after implant placement; R, range

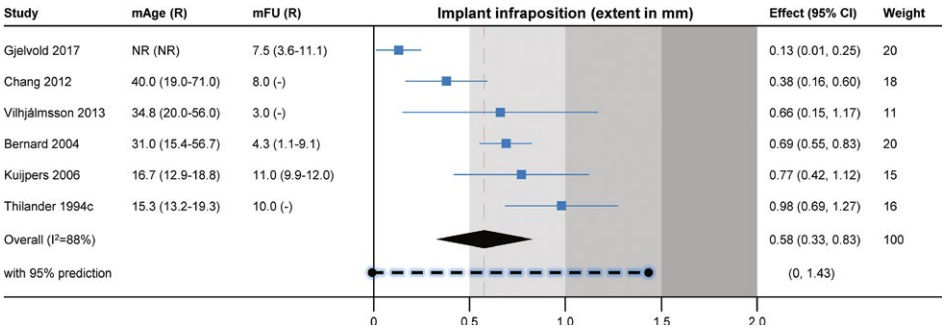

FIGURE 4 Contour enhanced forest plot of the pooled amount of implant infraocclusion in mm at implant level. CI, confidence interval; mAge, mean age at implant placement in year; mFU, mean follow-up in years after implant placement; R, range

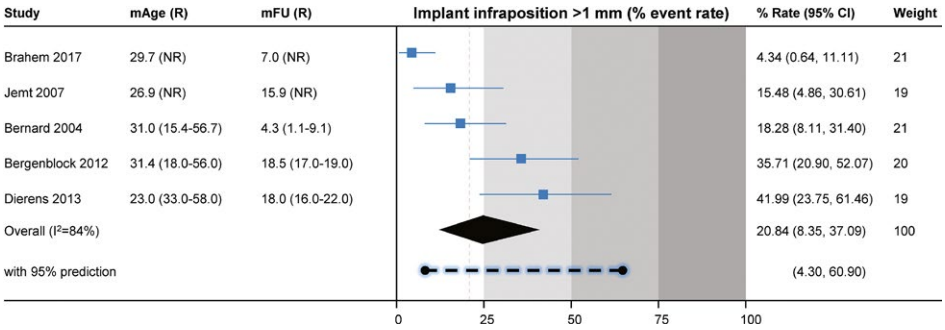

FIGURE 5 Contour enhanced forest plot of the pooled % event rate of considerable implant infraocclusion (>1 mm) at implant level. CI, confidence interval; mAge, mean age at implant placement in year; mFU, mean follow-up in years after implant placement; R, range

93% of studies), the basic study design (being retrospective in 85% of studies), the use of reliable outcome measurement methods (issues existing in 81% of studies), and the use of inadequate samples (in 74% of studies), which could influence the studies' results and their precision.

3.4 | Results of individual studies and data synthesis

All analyses are based on data extracted from the published reports of identified studies, which apart from aggregate data also included raw data on three occasions (Bernard et al., 2004; Kuijpers, de Lange & van Gool, 2006; Thilander et al., 1994) that were reanalyzed in Supporting Information Appendix S6a-c. The results of the Thilander et al. (1994) study indicated that patient age, skeletal maturation stage, and residual height growth all had a significant effect on the amount of observed IIP, with older/more skeletally mature patients having less IIP. Additionally, maxillary implants were tangentially more likely to experience considerable IIP (>1 mm) than mandibular ones.

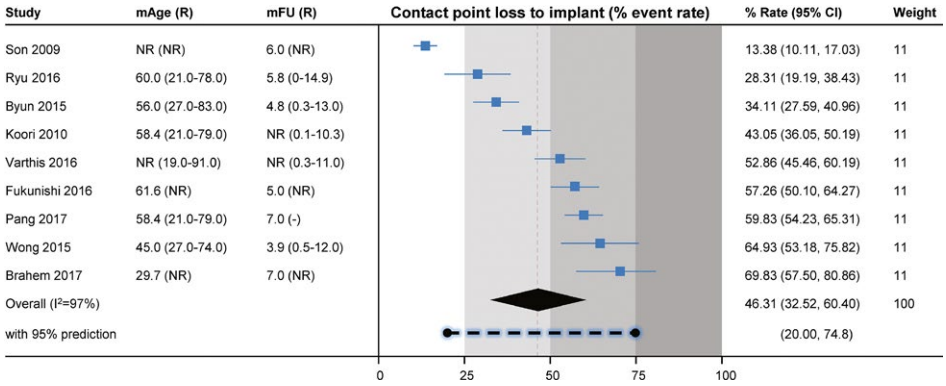

FIGURE 6 Contour enhanced forest plot of the pooled % event rate of proximal contact point loss at implant level. CI, confidence interval; mAge, mean age at implant placement in year; mFU, mean follow-up in years after implant placement; PCP, proximal contact point; R, range

As far as data synthesis is concerned, initially the average event rates or the average amounts of the primary and secondary outcomes were calculated across all studies through indirect random-effects meta-analyses (1-group pooling; Table 3). The results indicated that about half of placed implants show after average periods of 4.0- to 18.5-year signs of IIP (nine studies; pooled average rate of 50.5%; Figure 3) and the extent of which is on average at 0.58 mm (six studies; Figure 4). However, extreme heterogeneity existed across the identified studies, which led to a random-effects prediction of 10.4%–90.0% for the prevalence of IIP and a prediction of up to 1.43 mm for the extent of IIP. The pooled prevalence for IIP of considerable magnitude (IIP > 1 mm), again after an average follow-up of 4.3–18.5 years, was 20.8% (five studies; Figure 5), which meant that about every 5th implant placed will be in risk of considerable IIP at some time. For this analysis too, great heterogeneity was seen across studies, which led to a very imprecise future prediction for IPP > 1 mm prevalence of 4.3%–60.9%. Finally, as far as mesiodistal movements of the adjacent teeth are concerned, meta-analysis of nine studies indicated that the risk of PCP loss after mean observations of 3.9–7.0 years was 46.3% (Figure 6), which translated roughly to every second implant loosing a PCP. Similarly to the previous analyses, however, a wide random-effects prediction was calculated, which placed the PCP loss risk for a future implant somewhere between 20.0% and 74.8%, due to the extreme heterogeneity seen across the results of existing studies.

This heterogeneity observed across studies was attempted to be explained through various patient-, implant-, or study-related characteristics (Table 4). As such, implant placement jaw was significantly associated with IIP development, with IIP rate increasing parallel to an increasing proportion of implants placed in the maxilla ($p = 0.02$). Additionally, the extent of observed IIP was significantly associated with patient age, patient sex, placement jaw, and follow-up duration. This indicated that smaller amounts of IIP were observed for older patients and for male patients. Additionally, the amount of IIP observed was significantly associated with observation period, which averaged a 0.05 mm increase in IIP per year. Interestingly, the amount of IIP seem to decrease as the proportion of implants placed in the maxilla increased, which is contrary to the effect seen for the prevalence of IIP. However, a post hoc meta-regression indicated an association of mean age with % of implants placed in the maxilla across studies (11.7% increase of maxillary-placed implants for every 10 patient-years; $p < 0.001$), which could indicate a possible confounding effect. Finally, implantation area in terms of anterior jaw (up to the canine) or posterior jaw (from the premolar and posteriorly) was significantly associated with the risk of considerable IIP (>1 mm).

Insights into the effect of patient-, implant-, or study-related characteristics can be more robustly gleamed from the direct random-effects meta-analyses of these factors from within- and across-studies (2-groups' comparison; Table 5). Patient sex was confirmed as a significant factor for IIP, where male patients had lower odds for IIP than female patients (3 studies; OR = 0.3; 95% CI = 0.1–0.9). This is translated clinically to an NNT of 6 (95% CI = 3–77), which indicates that for every six implants placed in female patients, one more implant will have IIP than in male patients. A tendency for less IIP in the mandible compared with the maxilla was seen (MD = −0.21 mm), although this was marginally close to significance ($p = 0.07$). Apart from that, a significant influence was seen for follow-up duration and PCP side on the observed PCP loss, where the odds for PCP loss increased by about 10% each additional year the implant was in the mouth (2 studies; OR = 1.1; 95% 1.0–1.1) and implants had higher odds of losing their mesial PCP than their distal one (5 studies; OR = 2.3; 95% CI = 1.1–4.8). This would be translated to an NNT of 6 (95% CI = 3–91) and would indicate that for every 6th implant placed, one additional mesial PCP is lost over the loss rate of the distal PCP.

The GRADE approach was used to assess the quality of evidence originating from direct meta-analytical comparisons (Table 6). As analyses were done in an explorative fashion and multiple meta-analytical comparisons existed (Table 5), only comparisons with $p < 0.05$ were included in the GRADE approach (Table 6), where very

TABLE 4 Random-effects meta-regression on the event rates or average values of the primary and secondary outcomes (indirect data) at implant/tooth/contact point level. All data sets (pertaining to different follow-ups) are extracted from each study and all are included in the analyses

Outcome	Factor	Category	*n*	*b*	95% CI	*p*
IIP_{binary} % event rate	Age	Per year	9	−0.90%	−4.8 to 3.0	0.60
	Sex	% male (per 10%)	8	−11.20%	−35.1 to 12.7	0.29
	Follow-up	Per year	10	1.90%	−1.6 to 5.3	0.25
	Jaw*	% in maxilla (per 10%)	8	19.70%	5.1 to 34.3	**0.02**[*,a]
	Region	% anterior (per 10%)	9	5.50%	−1.6 to 12.6	0.11
$IIP_{continuous}$ extent in mm	Age	Per year	13	−0.02 mm	−0.03 to −0.01 mm	**0.001**[a]
	Sex	% male (per 10%)	12	−0.48 mm	−1.06 to 0.11 mm	**0.10**[a]
	Follow-up	Per year	14	0.05 mm	−0.01 to 0.10 mm	**0.08**[a]
	Jaw	% in maxilla (per 10%)	14	−0.11 mm	−0.22 to −0.01 mm	**0.04**[a]
	Region	% anterior (per 10%)	13	0.04 mm	−0.06 to 0.15 mm	0.41
IIP > 1 mm_{binary} % event rate	Age	Per year	5	−1.80%	−9.7 to 6.1	0.52
	Sex	% male (per 10%)	4	NC		
	Follow-up	Per year	5	1.60%	−1.4 to 4.7	0.19
	Jaw	% in maxilla (per 10%)	4	NC		
	Region	% anterior (per 10%)	5	−12.90%	−26.3 to 0.4	**0.05**[a]
PCP $loss_{binary}$ % event rate	Age	Per year	8	−0.40%	−1.5 to 0.6	0.34
	Sex	% male (per 10%)	8	−12.70%	−29.8 to 4.5	0.12
	Follow-up	Per year	8	0.50%	−16.8 to 17.7	0.95
	Jaw	% in maxilla (per 10%)	6	0.40%	−4.4 to 5.2	0.84
	Region	% anterior (per 10%)	8	1.20%	−2.8 to 5.2	0.50

b: unstandardized meta-regression coefficient; CI: confidence interval; IIP: infraposition of the implant restoration relative to adjacent teeth; NC: non-calculable; PCP: proximal contact point.

[a]Statistically significant meta-regression findings with $p < 0.10$.

*One study with 100% implant infraposition and zero variance (Jamilian 2015) was excluded to enable meta-regression.

low quality of evidence was found in all cases. This indicates that our confidence in these recommendations is limited and could be altered by future studies.

Finally, several patient-, implant-, or study-related characteristics were assessed within included studies, but as only one study contributed to each comparison, no meta-analysis could be performed (Supporting Information Appendix S7). Summarizing studies with results that were both statistically and clinically relevant, it was seen that IIP was greater in the anterior region (compared with the posterior region), in orthodontically treated patients (compared with not treated patients), and in skeletally young patients (compared with skeletally mature patients). As far as PCP is concerned, greater PCP loss was seen in patients over 60 years old (compared with patients between 20 and 39 years old), as well as for teeth with increased marginal bone loss (compared with no bone loss), with bone density D3–D4 according to Misch (compared with categories D1–D2), for single-rooted teeth (compared with multi-rooted teeth), for teeth with increased mobility (compared with teeth with normal mobility), and for teeth participating in lateral occlusal guidance (compared with nonparticipating teeth). However, only one study contributed to each factor and caution is warranted by the interpretation of these, until they are confirmed by future studies.

3.5 | Sensitivity analyses

Sensitivity analyses were attempted using the blinding of outcome assessment, but no identified study employed properly blinded assessors. Likewise, sensitivity analyses using only prospective studies were impossible, as 1–2 prospective studies were included at best in each meta-analysis, making comparisons unstable. A post hoc sensitivity analysis was conducted by including data on the patient level, instead of the implant level that was included in the main analysis (Supporting Information Appendix S8a,b), which indicated no important influence on effect estimation, precision, or heterogeneity. The only exception was the direct meta-analysis of IIP among male and female patients, where the sensitivity analysis found a smaller effect (RR of 0.7 compared with OR of 0.3), which was attributed to the ORs used in the main analysis that was adjusted for confounders. A post hoc sensitivity analysis including only studies with patients over 20 years old (judging by their inclusion criteria and age range) indicated similar results to the main analysis (Supporting Information Appendix S9). Finally, an a priori sensitivity analysis was attempted by including only large-scale studies (set as including at least 100 implants), but could only partially be conducted, and no discrepancies were found (Supporting Information Appendix S10).

TABLE 5 Meta-analyses of direct evidence (within- and across-studies) on the primary and secondary outcomes at implant/tooth/contact point level

Outcome	Reference	Experimental	*n*	Effect	95% CI	*p*	I^2, % (95% CI)	τ^2 (95% CI)	95% prediction
IIP_{binary}	Female	Male	3	OR = 0.29	0.10, 0.88	**0.03**[a]	0 (0, 98)	0 (0, 55.68)	0.39, 0.39
$IIP_{continuous}$	Central incisor	Lateral incisor	2	MD = 0.12	−0.21, 0.44	0.48	0 (0, 97)	0 (0, 3.16)	NA
$IIP_{continuous}$	Female	Male	3	MD = 0.00	−0.43, 0.44	1.00	70 (16, 99)	0.10 (0.01, 4.80)	−4.83, 4.83
$IIP_{continuous}$	Posterior region	Anterior region	2	MD = 0.19	−0.14, 0.52	0.25	34 (0, 100)	0.02 (0, 58.82)	NA
$IIP_{continuous}$	Maxilla	Mandibular	2	MD = −0.21	−0.44, 0.02	0.07	0 (0, 99)	0 (0, 3.23)	NA
$IIP > 1\ mm_{binary}$	Age over 20 years	Age under 20 years	2	RR = 2.13	0.98, 4.61	0.06	0 (0, 99)	0 (0, 65.58)	NA
$IIP > 1\ mm_{binary}$	Age over 25 years	Age under 25 years	2	RR = 1.77	0.82, 3.83	0.15	0 (0, 99)	0 (0, 58.45)	NA
$IIP > 1\ mm_{binary}$	Age over 30 years	Age under 30 years	2	RR = 2.33	0.95, 5.70	0.07	0 (0, 44)	0 (0, 0.36)	NA
$IIP > 1\ mm_{binary}$	Age over 30 years	Age between 25 and 30 years	2	RR = 1.32	0.47, 3.72	0.61	0 (0, 0)	0 (0, 0)	NA
$IIP > 1\ mm_{binary}$	Female	Male	2	RR = 0.62	0.28, 1.39	0.25	0 (0, 100)	0 (0, 159.14)	NA
$PCP\ loss_{binary}$	Adjacent tooth not splinted	Adjacent tooth splinted	2	OR = 0.6	0.19, 2.49	0.58	76 (0, 100)	0.65 (0, 873.51)	NA
$PCP\ loss_{binary}$	Adjacent tooth vital	Adjacent tooth nonvital	2	OR = 1.19	0.66, 2.17	0.56	29 (0, 100)	0.06 (0, 201.93)	NA
$PCP\ loss_{binary}$	Patient age in years		2	OR = 1.02	0.99, 1.05	0.16	0 (0, 100)	0 (0, 0.20)	NA
$PCP\ loss_{binary}$	Distal PCP	Mesial PCP	5	OR = 2.25	1.06, 4.77	**0.03**[a]	78 (25, 98)	0.56 (0.05, 6.30)	0.16, 32.53
$PCP\ loss_{binary}$	Female	Male	4	OR = 0.83	0.33, 1.10	0.19	0 (0, 89)	0 (0, 0.68)	0.44, 1.54
$PCP\ loss_{binary}$	Follow-up in years		2	OR = 1.09	1.03, 1.16	**0.004**[a]	0 (0, 0)	0 (0, 0)	NA
$PCP\ loss_{binary}$	Maxilla	Mandibular	5	OR = 1.32	0.84, 2.08	0.23	59 (7, 95)	0.15 (0.01, 1.82)	0.31, 5.62
$PCP\ loss_{binary}$	Molar	Premolar	2	OR = 0.84	0.40, 1.77	0.64	66 (0, 100)	0.19 (0, 293.97)	NA

CI: confidence interval; IIP: infraposition of the implant restoration relative to adjacent teeth; MD: mean difference; NC: not calculable; OR: odds ratio; PCP: proximal contact point; RR: relative risk.

[a]bold values indicate statistically significant subgroup/meta-regression findings with $p < 0.010$.

4 | DISCUSSION

4.1 | Summary of evidence

To our knowledge this is the first systematic review to summarize and assess in a systematic manner the late post-treatment complications of dental implants placed among natural teeth. The literature search yielded a total of 27 (mostly retrospective) nonrandomized studies including at least 1,572 patients (mean age 42.2 years/51.2% female) and at least 7,835 dental implants followed for up to 18.5 years postinsertion. The pooled % prevalence of IIP on tooth level was 50.5% (nine studies; 95% CI = 26.3–74.5%; Figure 3) and the pooled average IIP extent was 0.58 mm (six studies; 95% CI = 0.3–0.8 mm; Figure 4), while IIP > 1 mm was seen for 20.8% of placed implants (five studies; 95% CI = 8.3–37.1%; Figure 5). This indicated that both IIP on general and considerable IIP (>1 mm) are frequent complications of dental implants during their long-term function in the mouth. As stated before, this has been described by some authors as a response to sagittal or transversal growth of the jaws during adolescent and postadolescent active growth (Thilander et al., 1994). Indeed, reanalysis of available raw data indicated that the amount of IIP was directly associated with the skeletal maturation phase as gauged by hand-wrist radiographs and to the amount of residual height a patient attained through growth (Supporting Information Appendix S6b). However, the results were the same in the sensitivity analysis with the inclusion criterion of only patients ≥20 years old (Supporting Information Appendix S9), with IIP prevalence being 43% (including patients 27–63 years old), IIP extent being 0.44 mm (including patients 20–56 years old), IIP > 1 mm prevalence being 42% (including patients 33–58 years old), and PCP loss prevalence being 46% (including patients 21–83 years old). This indicates that both IIP and PCP are not limited in the active growth period of adolescence and early adulthood. Other studies have described that IIP can also be seen among mature adults with practically no active growth potential, as a response to 'slow growth' and the continuous eruption of natural teeth (Oesterle & Cronin, 2000). The available data from Bernard et al. (2004) corroborate this, as even patients older than 35 years showed definite signs of IIP (mean IIP of 0.67 mm and range of 0.12–1.86 mm for the 19 patients over 35 years).

As far as the extent of IIP is concerned, the results of existing studies were very heterogeneous, which was reflected in a random-effects prediction for IIP ranging from 0 to 1.43 mm (Table 3), and even IIPs of up to 1.86 or 2.00 mm have been reported (Supporting Information Appendix S6a–c). It seems that IIP is the result of a slow continuous process through time with an estimated mean increase of 0.05 mm per observation year (Table 4), which indicates that the combination of patient age and follow-up duration might explain some of the heterogeneity observed across studies. It seems therefore prudent that regular clinical examinations of placed implants take place to timely identify implant crowns with IIP, where action might be indicated (for example in terms of crown replacement).

Additionally, a significant influence of patient sex on IIP was found, which was supported by indirect (Table 4) and direct evidence (Table 5) and indicated that male patients were associated with milder IIP than female patients. This might be attributed to the more pronounced increase of anterior face height and posterior rotation of the mandible seen among female patients (Jemt, Ahlberg, Henriksson & Bondevik, 2007). Especially in late growth periods of 25–45 years of age, female patients seem to have greater increases in both overbite and upper anterior face height than male patients (Bishara & Jakobsen, 1998), which might explain at least in part this sex-specific difference in IIP.

Furthermore, no reliable evidence was found of a significant influence of preimplant orthodontic treatment on increased risk of IIP or PCP loss (Brahem, Holm, Sonnesen, Worsaae & Gotfredsen, 2017). Even though signs for increased risk of orthodontically treated patients for IIP (OR = 3.42), IIP > 1 mm (RR = 2.83), or PCP loss (OR = 2.97) were found (Supporting Information Appendix S7), these were not statistically significant ($p > 0.05$). Additionally, a potentially large difference in the amount of IIP was found between orthodontically treated and untreated patients (IIPs of 0.97 and 0.21 mm, respectively) by one study (Gjelvold et al., 2017). However, caution is warranted since the risk of confounding by indication is high, due to the nonrandomized design of included studies. To put it simply, patient receiving orthodontic treatment might present with more extreme craniofacial configurations in the vertical or sagittal plane and a potential for increased mandibular rotation than nonorthodontic patients, which might directly influence the observed IIP or PCP loss. Therefore, additional prospective studies are needed with either randomized design or statistical methods that minimize confounding in order to provide more conclusive evidence on the subject.

The influence of craniofacial morphology on the observed IIP has been previously suggested (Jemt et al., 2007), but remains currently unclear. This is based on the assumption that patients with slow continuous posterior rotation of the mandible, combined with slow increase of anterior face height, would present a more "long-face" appearance in combination with greater infraposition of single-implant restorations in relation to adjacent anterior teeth in the upper jaw. However, this was not formally confirmed from the single study on the matter (Andersson, Bergenblock, Fürst & Jemt, 2013), even though long-face patients tended to have higher IIP odds than normal-face patients (OR = 2.14; $p = 0.42$). This needs to be assessed in the future with robust methodology (for example through cephalometric analysis), as only a subjective evaluation of face shape was performed in the currently existing study.

As far as the review's secondary outcome of PCP loss is concerned, a likewise high prevalence of 46.3% was found (Table 3; Figure 6), which indicated that almost every second implant might be in risk. Open PCPs of implant restorations have been associated with increased patient discomfort (Jeong & Chang, 2015; Ryu, 2016), which might be attributed to the increased food impaction between teeth (Jeong & Chang, 2015), reduced fill of the proximal spaces by the papilla (Jeong & Chang, 2015), and periodontal health (Jernberg et al., 1983). Also, similar to IIP, the process of PCP loss seemed to be a continuous procedure, with its prevalence increasing with

TABLE 6 Summary of findings table according to the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach

Outcome Trials (patients)	Relative effects (95% CI)	Anticipated absolute effects[a] (95% CI)			Quality of the evidence (GRADE)[c]	What happens
		CTR	EXP	Difference		
		Female	Male			
IIP 3 studies (88 patients)	OR 0.3 (0.10–0.88)	89.3%[b]	70.8% (45.5–88.0)	18.5% fewer implants (1.3–43.8 fewer)	⊕OOO very low[d] due to bias	Lower IIP incidence among male patients
		Distal PCP	Mesial PCP			
PCP loss 5 studies (573 patients)	OR 2.3 (1.06–4.77	24.1%[b]	41.7% (25.2–60.2)	17.6% more PCPs (1.1–36.1 more)	⊕OOO very low[d] due to bias	Greater incidence of PCP loss on the mesial side of the implant
		Baseline year	Per extra year			
PCP loss 2 studies (229 patients)	OR 1.1 (1.03–1.16)	45.7%[b]	47.8% (46.4–49.4)	2.1% more PCPs (0.7–3.7 more)	⊕OOO very low[d] due to bias	Incidence of PCP loss increases each year

Factors associated with implant infraposition or proximal contact point loss.
Population & intervention: adolescent/adult patients receiving dental implant treatment.
Settings: university clinics, private practices, and clinics (Japan, South Korea, Sweden).
CI, confidence interval; CTR, control category; EXP, experimental category; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IIP, implant infraposition; OR, odds ratio; PCP, proximal contact point.
[a]The basis for the risk in the control group (e.g., the median control group risk across studies) is provided in footnotes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [b]Response in the control group is based on average event rate of included studies in each case. [c]GRADE for both randomized and nonrandomized studies starts from "high". [d]Downgraded initially to "low" due to the lack of randomization; further downgraded to very low for lack of blinding serious limitations (high risk of bias).

each follow-up year (Table 5; OR = 1.09) and with the time of half occurrence being reported between 3.0 years (Pang et al., 2017) or 5.5 years postinsertion (Koori, Morimoto, Tsukiyama & Koyano, 2010).

There was a clear predilection of PCP loss for the mesial PCP of implant-supported prostheses over the distal ones (Table 5), which remained after including only bounded cases of restorations (i.e., having both mesial and distal PCPs with natural teeth; Pang et al., 2017). This has been attributed to mesial drifting of the teeth mesially to the implant restoration mesial components of the occlusal forces (Heij et al., 2006; Koori et al., 2010; Wat, Wong, Leung & Pow, 2011). Finally, marginal bone loss of the adjacent tooth was significantly associated with PCP loss (Pang et al., 2017), which could be explained by an increased mesial dislocation of the tooth under occlusal forces (Wei et al., 2008). All these indicate that the physiological or increased mobility of the natural adjacent teeth in combination with the anterior or lateral force components of mastication might play an important role in PCP loss of the implant-supported reconstruction.

4.2 | Strengths and limitations

The strengths of this systematic review consist of the registration of its a priori protocol in PROSPERO (Sideri, Papageorgiou & Eliades, 2018), its exhaustive literature search, its improved analytical methods (Petropoulou and Mavridis, 2017; Veroniki et al., 2016), the use of the GRADE approach (Guyatt et al., 2011) to assess the quality of the meta-evidence, and the transparent provision of the study's data (Papageorgiou et al., 2018). However, certain limitations also exist. First and foremost, this systematic review included only nonrandomized trials that are at higher risk of bias than randomized ones (Papageorgiou, Kloukos, Petridis & Pandis, 2015b). As the scope of the review pertained more to adverse effects and diagnosis, nonrandomized designs might be applicable, but the vast majority of included studies (85%) were retrospective and therefore at higher risk of bias than prospective studies (Papageorgiou, Xavier, Cobourne, 2015). Additionally, methodological issues existed for all included studies, as has been often reported for clinical trials in prosthodontics and implant dentistry (Papageorgiou, Kloukos, Petridis & Pandis, 2015a), and these might have influenced the review's results. Furthermore, the identified studies were predominantly small and this might introduce small-study effects (Cappelleri et al., 1996). Finally, the limited number of included studies and their suboptimal reporting did not enable robust assessments of heterogeneity, as well as the conduct of several analyses for subgroup, small-study effects, and reporting biases that were planned.

5 | CONCLUSIONS

Based on a limited number of mostly small to medium nonrandomized studies on the long-term performance of implant-supported restorations among natural teeth, it seems that about every second

implant is affected by IIP and PCP loss during its first 5–15 years of life. However, high heterogeneity exists among the results of existing studies, which make accurate predictions about the risk and extent of these adverse effects difficult. There is some scant evidence about increased risk of IIP for female patients and increased risk of PCP loss for the mesial side of the implant, but the quality of evidence is very low. Given the high prevalence of both IIP and PCP loss and their potential influence on patient satisfaction, further research on the minimization and treatment of IIP and PCP loss is advised, which should, however, be utilized using well-controlled prospective blinded study designs with higher internal validity than existing studies.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

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